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# Understanding the Risks of Immunosuppression Reduction for Active COVID-19 Infection



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Kidney transplant recipients (KTRs) are at higher risk of mortality and morbidity from COVID-19 infection compared with the general population.[1] Some of this elevated risk comes from nonmodifiable factors common to KTRs, such as diabetes, hypertension, and chronic kidney disease. However, transplant immunosuppression is a theoretically modifiable risk factor. Though better studied in the setting of COVID-19 vaccination rather than active COVID-19 infection, immunosuppressed patients are less likely to mount a T-cell response measured via ELISPOT assay and less likely to mount a robust, durable antibody response.[2] This is particularly true for patients on mycophenolate or belatacept. There is some evidence to support the intuitive idea that reduction in immunosuppression helps transplant recipients develop a more robust anti–COVID-19 immune response. In at least 1 study, transplant recipients who underwent immunosuppression reduction in the setting of active infection had the ability to generate interferon-γ–secreting CD3+ T cells against SARS-CoV-2 peptides and generate anti–S protein and anti–N protein IgG, presumably markers of cellular and humoral immunity against COVID-19, respectively.[3] Alternatively, underimmunosuppression, whether through patient noncompliance or physician directed, is associated with rejection and the development of *de novo* donor-specific anti–human leukocyte antigen antibodies (dnDSAs).[4]

Balancing the risk of immunosuppression reduction with the potential benefits is quite challenging and carried out on a case-by-case basis depending on the severity of COVID-19 infection. A common approach among clinicians is to stop antiproliferative agents in moderate COVID-19 infection and discontinue or reduce the dose of calcineurin inhibitors in more severe cases.[5] In a systematic review involving 420 adult KTRs, reduction or discontinuation of immunosuppression was observed in 58% of the patients and antimetabolites and calcineurin inhibitors were discontinued in 91% and 58% of KTRs, respectively.[6] Undoubtedly, in light of a number of recent publications, our knowledge regarding graft outcomes, rejections, and mortality in KTRs following COVID-19 infection has taken a huge leap. However, the question concerning the effect of immunosuppression modulation on the development of human leukocyte antigen antibodies after SARS-CoV-2 (COVID-19) infection is still unanswered. Vásquez-Jiménez *et al.*[7] did a follow-up of 4 weeks in 20 KTRs after COVID-19 infection and performed anti–human leukocyte antigen antibody testing to screen for dnDSA and kidney graft biopsy. The analysis showed the development of dnDSA in 11 patients (class I in 2 patients, class II in 6 patients, and both classes I and II in 3 patients). Of these 11 patients, 27.2% had antibody-mediated rejection, 36.4% mixed antibody-mediated rejection and T-cell mediated rejection, and 36.4% chronic antibody-mediated rejection. However, the possibility of the presence of dnDSA before the COVID-19 diagnosis could not be ruled out and a lack of serial renal biopsies rendered it difficult to draw any cause-effect relationship. Another analysis by Pampols *et al.*[8] including 47 KTRs with 3 months of follow-up after COVID-19 infections failed to demonstrate any appearance of dnDSA or rejection episodes despite reduction in immunosuppressive medications for a median time of 17 days.

In this context, Masset *et al.*[9] provided a retrospective cohort analysis of 179 KTRs following COVID-19

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infection from 2 French institutions. The authors assessed the occurrence of dnDSA in addition to allograft rejection and graft loss following COVID-19. Of note, almost half of the patients (49.2%) were hospitalized and interruption of antimetabolites was done in 47% (82% in hospitalized and 15% in nonhospitalized patients). The median time of resumption of the antimetabolites was 23 days and 7 days in hospitalized and nonhospitalized patients, respectively. Furthermore, calcineurin inhibitors were interrupted in 12% of the KTRs.

Before COVID-19 infection, screening for dnDSA had been done at a median of 212 days (range 2–701 days). Post–COVID-19 dnDSA screening was performed at a median of 45 days (range 4–412 days). The authors demonstrated that the incidence of dnDSA after COVID-19 infection was 4% overall and 8% in hospitalized patients. Allograft rejection was detected in 3 patients (1.7%), but there was no immunologic-related graft loss. The occurrence of post–COVID-19 dnDSA was associated with younger age, the onset of infection within the first year after transplantation, and a history of pre-existing DSA (different from the dnDSA) before transplantation. Surprisingly, there was no impact of raised inflammatory markers, such as interleukin-6 and C-reactive protein levels, total lymphocyte count, the severity of COVID-19, and the use of antiviral therapies.

The results of the study support the findings of TANGO cohort analysis in which no survival benefit of immunosuppression interruption in KTRs with COVID-19 infection was observed.[10] Although the study did not reveal any higher incidence of post–COVID-19 dnDSA appearance despite the substantial reduction of immunosuppression suggesting that COVID-19 itself may not be a major immunologic trigger, some issues remain to be addressed. The absence of systematic protocol biopsies during ongoing COVID-19 infection at the time of immunosuppression interruption might have underestimated the alloimmune response and subclinical rejections. Because the screening of dnDSA after COVID-19 infection was done at variable intervals of time, the status of immediate post–COVID-19 dnDSA changes that may have been transient remains unknown. It is difficult to know about the ongoing immunologic response in asymptomatic patients with COVID-19. In addition, any inference of the results is challenged by the retrospective nature of the published studies.

In summary, Masset *et al.*[9] provide an interesting analysis indicating that risks of the development of post–COVID-19 DSA, allograft rejection, and graft loss are low and are mainly restricted to high-risk immunologic patients and those with severe disease requiring hospitalization and/or elimination of calcineurin inhibitor. Hence, a transient interruption or modulation of immunosuppression in COVID-19–infected KTRs for a short period of time seems safe and can be applied according to the COVID-19 severity. However, long-term prospective studies with a large cohort group are warranted.

## DISCLOSURE

All the authors declared no competing interests.

## REFERENCES


1. Thaunat O, Legeai C, Anglicheau D, et al. IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT). *Kidney Int*. 2020;98:1568–1577. https://doi.org/10.1016/j.kint.2020.10.008
2. Chavarot N, Ouedrani A, Marion O, et al. Poor anti-SARS-CoV-2 humoral and T-cell responses after 2 injections of mRNA vaccine in kidney transplant recipients treated with Belatacept. *Transplantation*. 2021;105:e94–e95. https://doi.org/10.1097/TP.0000000000003784
3. Candon S, Guerrot D, Drouot L, et al. T cell and antibody responses to SARS-CoV-2: experience from a French transplantation and hemodialysis center during the COVID-19 pandemic. *Am J Transplant*. 2021;21:854–863. https://doi.org/10.1111/ajt.16348
4. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12:388–399. https://doi.org/10.1111/j.1600-6143.2011.03840.x
5. Maggiore U, Abramowicz D, Crespo M, et al. How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion. *Nephrol Dial Transplant*. 2020;35:899–904. https://doi.org/10.1093/ndt/gfaa130
6. Marinaki S, Tsiakas S, Korogiannou M, et al. A systematic review of COVID-19 infection in kidney transplant recipients: a universal effort to preserve patients' lives and allografts. *J Clin Med*. 2020;9:2986. https://doi.org/10.3390/jcm9092986
7. Vásquez-Jiménez E, Moguel-Gonzalez B, Soto-Abraham V, Flores-Gama C. Risk of acute rejection in kidney transplant recipients after COVID-19. *J Nephrol*. 2022;35:367–369. https://doi.org/10.1007/s40620-021-01192-x
8. Pampols PA, Trujillo H, Melilli E, et al. Immunosuppression minimization in kidney transplant recipients hospitalized for COVID-19. *Clin Kidney J*. 2021;14:1229–1235. https://doi.org/10.1093/ckj/sfab025
9. Masset C, Gautier-Vargas G, Cantarovich D, et al. Occurrence of *de novo* donor-specific antibodies after COVID-19 in kidney transplant recipients is low despite immunosuppression modulation. *Kidney Int Rep*. 2022;7:983–992.
10. Cravedi P, Mothi SS, Azzi Y, et al. COVID-19 and kidney transplantation: results from the TANGO International Transplant Consortium. *Am J Transplant*. 2020;20:3140–3148. https://doi.org/10.1111/ajt.16185